

AMENDMENT TO THE CLAIMS

- 1-4. (Canceled)
5. (Currently Amended) An adzyme for enzymatically altering a substrate, the adzyme being a fusion protein comprising: a [[catalytic]] protease domain that cleaves at least one peptide bond of said substrate to produce one or more products, and a polypeptide targeting domain that reversibly binds with an address site on said substrate or with an address site on a second molecule that occurs in functional proximity to the substrate, wherein
- wherein said targeting domain and said protease domain are discrete and heterologous with respect to each other,
- ~~said adzyme is resistant to cleavage by the catalytic domain,~~
- said targeting domain, when provided separately, binds to the substrate,
- said [[catalytic]] protease domain, when provided separately, cleaves at least one peptide bond of said substrate to produce one or more products, and
- ~~said adzyme is more potent than said catalytic domain or targeting moiety with respect to the reaction with said substrate,~~
- wherein the substrate is a biomolecule in a biomolecular accretion.
6. (Canceled)
7. (Previously Presented) The adzyme of claim 5, wherein the substrate is endogenous to a human patient.
8. (Previously Presented) The adzyme of claim 7, wherein the adzyme is effective against the substrate in the presence of physiological levels of human serum protein.
9. (Previously Presented) The adzyme of claim 8, wherein the human serum protein is human serum albumin.
- 10-25. (Canceled)
26. (Currently Amended) The adzyme of claim 5 [[25]], wherein said fusion protein includes a linker between said [[catalytic]] protease domain and said targeting domain.
27. (Previously Presented) The adzyme of claim 26, wherein said linker is an unstructured peptide.

28. (Canceled)
29. (Original) The adzyme of claim 27, wherein said linker includes one or more repeats of Ser₄Gly or SerGly₄.
30. (Canceled)
31. (Currently Amended) The adzyme of claim 26, wherein said linker is selected to provide steric geometry between said catalytic domain and said targeting domain such that said adzyme is more active [[potent]] than said catalytic domain or targeting domain with respect to the reaction with said substrate.
- 32-34. (Canceled)
35. (Currently Amended) The adzyme of claim 5 [[25]], wherein the fusion protein is a cotranslational fusion protein encoded by a recombinant nucleic acid.
36. (Canceled)
37. (Currently Amended) The adzyme of claim 5, wherein the ~~substrate is a biomolecule~~ is produced by a cell.
- 38-47. (Canceled)
48. (Currently Amended) The adzyme of claim 5 [[47]], wherein the biomolecular accretion is selected from among: an amyloid deposit and an atherosclerotic plaque.
49. (Currently Amended) The adzyme of claim 5 [[37]], wherein the biomolecular accretion is ~~biomolecule is a biomolecule~~ produced by a pathogen.
50. (Currently Amended) The adzyme of claim 49, wherein the pathogen is ~~selected from among;~~ a protozoan, a fungus, a bacterium, or [[and]] a virus.
51. (Currently Amended) The adzyme of claim 5 [[37]], wherein the biomolecular accretion comprises ~~biomolecule is a~~ prion protein.
- 52-55. (Canceled)
56. (Withdrawn, Currently Amended) The adzyme of claim 5 [[52]], wherein said protease is a zymogen.
57. (Canceled)

58. **(Currently Amended)** The adzyme of claim 5 [[52]], wherein said adzyme is purified from a cell culture in the presence of a reversible protease inhibitor.

59-68. **(Canceled)**

69. **(Currently Amended)** The adzyme of claim 5, wherein the adzyme is resistant to cleavage by the [[catalytic]] protease domain at an adzyme concentration that is about equal to the concentration of adzyme in a solution to be administered to a subject.

70. **(Currently Amended)** The adzyme of claim 5 [[37]], wherein said adzyme alters the half-life of the biomolecule *in vivo*.

71. **(Canceled)**

72. **(Currently Amended)** The adzyme of claim 5 [[37]], wherein said adzyme alters the distribution of the biomolecule *in vivo*.

73. **(Canceled)**

74. **(Currently Amended)** The adzyme of claim 5 [[37]], wherein said adzyme reduces a biological activity of said biomolecule.

75. **(Canceled)**

76. **(Currently Amended)** The adzyme of claim 5 [[37]], wherein said biomolecule binds a plurality of different molecules *in vivo*, and said adzyme alters the binding specificity of said biomolecule.

77. **(Canceled)**

78. **(Currently Amended)** The adzyme of claim 5 [[37]], wherein said adzyme alters the interaction of said biomolecule with other molecules *in vivo*.

79-106. **(Canceled)**

107. **(Previously Presented)** The adzyme of claim 5, wherein the targeting domain is an antibody or polypeptide(s) including an antigen binding site thereof.

108. **(Previously Presented)** The adzyme of claim 107, wherein the targeting domain is selected from the group consisting of a monoclonal antibody, an Fab and F(ab)₂, an scFv, a heavy chain variable region and a light chain variable region.

109. **(Canceled)**

110. **(Withdrawn)** The adzyme of claim 5, wherein said targeting domain is an artificial protein or peptide sequence engineered to bind to said substrate.
- 111-116. **(Canceled)**
117. **(Currently Amended)** The adzyme of claim 5 ~~[[115]]~~, wherein the protease is selected from among: MT1-MMP; MMP12; tryptase; MT2-MMP; elastase; MMP7; chymotrypsin; and trypsin.
- 118-126. **(Canceled)**
127. **(Previously Presented)** An adzyme preparation for therapeutic use in a human patient, the preparation comprising an adzyme of claim 5.
128. **(Original)** The adzyme preparation of claim 127, further comprising a pharmaceutically effective carrier.
129. **(Original)** The adzyme preparation of claim 127, wherein the adzyme preparation is formulated such that autocatalytic modification of the adzyme is inhibited.
130. **(Canceled)**
131. **(Currently Amended)** The adzyme preparation of claim 127 ~~[[130]]~~, further comprising a reversible inhibitor of said protease.
132. **(Original)** The adzyme preparation of claim 131, wherein the reversible inhibitor is safe for administration to a human patient.
133. **(Original)** The adzyme preparation of claim 127, wherein said adzyme preparation is substantially pyrogen free.
134. **(Original)** The adzyme preparation of claim 127, wherein said adzyme preparation is packaged with instructions for administration to a patient.
135. **(Withdrawn)** A method of making a medicament for use in treating a disorder that is associated with an activity of the substrate of an adzyme of claim 5, the method comprising formulating the adzyme for administration to a human patient.
136. **(Canceled)**

137. **(Withdrawn)** A method of treating a disorder that is associated with an activity of the substrate of an adzyme of claim 5, the method comprising administering a therapeutically effective dose of the adzyme to a human patient in need thereof.

138-146. **(Canceled)**

147. **(Withdrawn)** A method for manufacturing an adzyme, the method comprising

- a) culturing a cell comprising an expression vector comprising a nucleic acid encoding the adzyme of claim 5, in conditions that cause the cell to produce the adzyme; and
- b) purifying the adzyme to substantial purity.

148-149. **(Canceled)**

150. **(Withdrawn)** The method of claim 147, wherein the purifying the adzyme to substantial purity includes the use of a reversible inhibitor that inhibits autocatalytic activity of the catalytic domain.

151-155. **(Canceled)**

156. **(Currently Amended)** The adzyme of claim 5, wherein the targeting moiety comprises a polypeptide or polypeptide complex.

157. **(New)** The adzyme of claim 5, wherein the adzyme is resistant to autocatalysis.